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## Incomplete reversibility of eGFR following tenofovir exposure

Sophie Jose<sup>1</sup>, Lisa Hamzah<sup>2</sup>, Lucy Campbell<sup>2</sup>, Teresa Hill<sup>1</sup>, Martin Fisher<sup>3</sup>, Clifford Leen<sup>4</sup>, Richard Gilson<sup>5</sup>, John Walsh<sup>6</sup>, Mark Nelson<sup>7</sup>, Phillip Hay<sup>8</sup>, Margaret Johnson<sup>9</sup>, David Chadwick<sup>10</sup>, Dorothea Nitsch<sup>11</sup>, Rachael Jones<sup>7</sup>, Caroline Sabin<sup>1</sup> and Frank Post<sup>2</sup>, on behalf of the UK Collaborative HIV

### Cohort Study Steering Committee

<sup>1</sup>Research Department of Infection and Population Health, UCL, London, UK

<sup>2</sup>Kings College Hospital NHS Foundation Trust and King's College London School of Medicine, London, UK

<sup>3</sup>Brighton and Sussex University Hospitals NHS Trust, Brighton, UK

<sup>4</sup>The Lothian University Hospitals NHS Trust, Edinburgh, UK

<sup>5</sup>Mortimer Market Centre, University College Medical School, London, UK

<sup>6</sup>Imperial College Healthcare NHS Trust, London, UK

<sup>7</sup>Chelsea & Westminster NHS Foundation Trust, London, UK

<sup>8</sup>St George's Healthcare NHS Trust, London, UK

<sup>9</sup>Royal Free Hospital, London, UK

<sup>10</sup>South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK

<sup>11</sup>London School of Hygiene and Tropical Medicine, London, UK

Corresponding Author: Miss Sophie Jose, Research Department of Infection and Population Health, UCL, Royal Free Campus, Rowland Hill Street, London NW3 2PF, Telephone 02077940500 ext. 36763, Email: [sophie.jose@ucl.ac.uk](mailto:sophie.jose@ucl.ac.uk)

**Abstract**

*Background:* Tenofovir disoproxil fumarate (TDF) has been linked to renal impairment but the extent to which this impairment is reversible is unclear. We aimed to investigate the reversibility of renal decline on TDF.

*Methods:* Cox Proportional Hazards models assessed factors associated with discontinuing TDF in those with >6 months exposure. In those who discontinued TDF, linear piecewise regression models estimated eGFR slopes (mL/min/1.73m<sup>2</sup>/yr) before, during and after TDF exposure. Factors associated with not achieving eGFR recovery 6 months after discontinuing TDF were assessed using multivariable logistic regression.

*Results:* We observed eGFR declines during TDF exposure (mean (95% CI) slopes -15.7 (-20.5, -10.9) during the first 3 months; -3.1(-4.6, -1.7) thereafter), and evidence of eGFR increases following discontinuation (12.5 (8.9, 16.1) during the first 3 months; 0.8 (0.1, 1.5) thereafter). Following TDF discontinuation, 38.6% of patients with eGFR decline did not experience recovery. A higher baseline eGFR, lower discontinuation eGFR and more prolonged TDF exposure were associated with increased risk of incomplete recovery at 6 months post-TDF discontinuation.

*Conclusions:* This study shows that eGFR decline on TDF was not fully reversible in one third of patients, and suggests that prolonged TDF exposure at low eGFR should be avoided.

## Introduction

Tenofovir disoproxil fumarate (TDF) is a widely used component of combination antiretroviral therapy (cART)<sup>1-3</sup>. Whilst clinical trial data indicate a low incidence of serious renal adverse effects<sup>4-6</sup>, cohort studies have linked TDF use to decreasing estimated glomerular filtration rate (eGFR)<sup>7</sup>, accelerated eGFR decline<sup>8</sup>, proximal tubular dysfunction<sup>9,10</sup>, proteinuria<sup>11</sup>, chronic kidney disease (CKD)<sup>12-14</sup> and increased mortality<sup>15</sup>. Scherzer et al.<sup>12</sup> evaluated the effects of TDF exposure on renal outcomes in 10,000 HIV treatment naive patients and found each year of cumulative exposure was associated with a 30% increase in the risk of proteinuria, an 11% increase in the risk of rapid eGFR decline ( $>3$  [ml/min/1.73m<sup>2</sup>]) and a 33% increase in the risk of developing CKD. The authors suggest that the effect of TDF was not fully reversible after discontinuation.

Studies exploring the reversibility of renal function decline following TDF discontinuation have focused on individuals stopping for toxicity<sup>16-20</sup>, but were small in size with inconclusive outcomes. Wever et al.<sup>20</sup> and Yoshino et al.<sup>21</sup> studied predominantly HIV positive men who discontinued TDF for incident CKD or a low eGFR (median IQR 48.3, 45.3-54.3) and found that only 42% of 45 patients recovered their baseline eGFR. The majority of individuals had impaired renal function at the start of TDF exposure, and some continued to experience eGFR decline following TDF discontinuation. Bonjoch et al.<sup>22</sup> looked at individuals with normal renal function at baseline who discontinued for toxicity and found that 59% had complete normalisation of eGFR.

There are few studies investigating changes in renal function with TDF using eGFR slopes and those that did, did not take into account the rate of renal decline pre-TDF exposure<sup>23</sup>. Fafin et al.<sup>24</sup> studied the evolution of eGFR in patients with CKD and observed that TDF exposure was associated with eGFR decline, and longer TDF exposure was associated with lower eGFR. Kalayjian et al.<sup>25</sup> examined eGFR slopes before and after initial cART exposure. Whilst there remained an overall eGFR decline on cART, this was modest and slower than pre-cART (0.81 (95% CI 0.03-1.59) p=0.02). In addition, when eGFR slopes were stratified by regime, a significant improvement was seen in those on TDF co-administered with a protease inhibitor (PI).

Our aim was to evaluate changes in renal function before, during and after TDF exposure using eGFR slopes in HIV-positive individuals who discontinued TDF. We also examined the extent to which eGFR decline with TDF was reversible following TDF discontinuation, accounting for pre-existing renal decline, and the factors associated with incomplete eGFR reversibility.

## Methods

### *Patients*

Data were obtained from the UK Collaborative HIV Cohort (UK CHIC) Study which collates routinely collected data on HIV positive individuals >16 years age from several of the largest HIV clinics in the UK<sup>26</sup>. The study was approved by a multicentre research ethics committee and by local ethics committees and does not require informed consent. Data up to December 2010 were available from nine centres that routinely provided creatinine measurements. Eligible subjects were exposed to TDF for a period of at least six months. The first available TDF episode of >6 months duration was used. Patients who discontinued TDF were included in the analysis of eGFR slopes and those whose eGFR declined on TDF were analysed for recovery. For the analysis of eGFR slopes and recovery, individuals were required to have at least six months TDF-free follow-up and three or more serum creatinine measurements before, during and after TDF exposure.

### *Variable definitions*

Serum creatinine measurements were converted to eGFR and expressed as ml/min/1.73m<sup>2</sup> using the CKD Epidemiology Collaboration (CKD-EPI) equation<sup>27,28</sup>. Where a patient's eGFR slope before TDF was <0, this indicated pre-existing eGFR decline. Recovery was then defined differently for those with and without evidence of pre-existing eGFR decline. Where there was pre-existing decline, we predicted eGFR at TDF discontinuation using pre-TDF eGFR slope and duration of TDF exposure and recovery was defined at the first of two consecutive eGFR within 5% of this predicted eGFR. For

those without evidence of decline prior to TDF exposure, recovery was defined at the first of two consecutive eGFR within 5% of eGFR at TDF start (baseline). Sensitivity analyses allowed for greater within-patient variability by changing this 5% cut off to 10% and 15%. Anyone who did not recover eGFR was deemed to have incomplete recovery. Normal eGFR refers to an eGFR >90.

### *Statistical Analysis*

Factors associated with discontinuation of TDF after six months were investigated with Cox proportional hazards models. Time dependent covariates considered were age, AIDS-defining events, CD4 count, viral load, ART regimen (NNRTI-based, PI-based including Atazanavir, PI-based not Atazanavir and other regimens), eGFR, Hepatitis B and Hepatitis C status. Time-independent covariates included sex, ethnicity, exposure, previous ART exposure (ART-naïve, experienced with no prior TDF exposure, experienced with prior TDF exposure) and calendar year of TDF start. All covariates with  $p < 0.1$  in univariable analysis considered for entry into the multivariable model.

In subjects who discontinued TDF, changes in eGFR before, during and after TDF exposure were investigated. Separate piecewise linear regression models were fitted for each patient, to estimate eGFR slopes in the three periods. eGFR slopes during and post-TDF exposure were split into two periods: <3months and >3months (Supplementary Figure 1). This was to separate any effect of residual drug exposure and early tubular creatinine secretion from longer term slope estimates. Slopes were stratified according to baseline eGFR <60, 60-89 and >90.

Factors associated with incomplete eGFR recovery at 6 months post-TDF discontinuation were assessed using logistic regression. Factors considered for inclusion in the model were eGFR at TDF start and discontinuation, time exposed to TDF, CD4 count and HIV viral load at start and discontinuation of TDF, being ART naïve at TDF start, cART regimen (PI vs. NNRTI vs. other) and demographics. Covariates considered for entry in the multivariable model were chosen a priori as

possible confounders or with  $p < 0.1$  in univariable analyses. Analyses were stratified by baseline eGFR to determine if starting or stopping TDF with an eGFR within the normal range influenced recovery. Sensitivity analyses considered factors associated with incomplete recovery out to 12 and 24 months. We also assessed recovery in those most likely to have discontinued for toxicity by excluding those with a detectable viral load at TDF discontinuation. All analyses were performed in SAS (version 9.3).

## Results

In total, 13,007 were included in the analysis (Figure 1). Baseline characteristics of these individuals are described in Table 1. The majority were white men who acquired HIV through sex with other men; 34.4% were ART naive at TDF start.

### *Factors associated with TDF discontinuation*

A total 3,088 (23.7%) patients discontinued TDF; an incidence rate (95% CI) of 7.3 (7.0, 7.5) per 100 person years. Median (IQR) exposure time was 2.6 (1.5, 4.8) years. eGFR decline during TDF exposure was experienced by 1,882 (61%) individuals who discontinued TDF and 56.3%, 21.0%, 12.3% and 10.3% discontinued TDF with an eGFR  $>90$ , 75-89, 60-74 and  $<60$  respectively. This compared to 65.6%, 22.2%, 9.8% and 2.4% in the same eGFR thresholds at baseline. Of 2,906 individuals with a viral load measure prior to stopping TDF, 2049 (70.5%) had an undetectable viral load. Higher viral load (Hazard Ratio (HR) 1.6, 95% confidence interval (CI) 1.55, 1.66) per 1  $\log_{10}$  increase) and lower eGFR (eGFR 60-74 HR 1.21, 95% CI 1.08, 1.25; eGFR  $<60$  HR 3.90, 95% CI 3.45, 4.42) were associated with increased risk of TDF discontinuation. ART-experience without prior TDF exposure was associated with decreased likelihood of discontinuation over ART-naïve individuals (HR 0.78, 95% CI 0.71, 0.86), whereas ART-experience including previous TDF use showed an increased likelihood (HR 1.24, 95% CI 1.07, 1.44). Higher CD4 cell count (HR 0.99, 95% CI 0.98, 0.99 per 50 cells/mm<sup>3</sup> increase), co-administration of TDF with an NNRTI (HR 0.56, 95% CI 0.50, 0.63) and a

previous AIDS event (HR 0.83, 95% CI 0.77, 0.90) were associated with decreased likelihood of TDF discontinuation (Supplementary Table 1).

#### *Changes in eGFR pre, during and post TDF exposure*

Of 3,088 patients who discontinued TDF, 834 (27.0%) had sufficient follow-up time and creatinine data to be included in analyses of eGFR slopes. Those included were more likely to be white ( $p<0.0001$ ), men who have sex with men ( $p<0.0001$ ), with higher CD4 cell counts ( $p<0.0001$ ), lower viral loads ( $p<0.0001$ ), be cART naïve at TDF start ( $p<0.0001$ ), have started TDF in an earlier year ( $p<0.0001$ ) and experienced a previous AIDS event ( $p=0.0003$ ).

Median (IQR) follow-up before, during and after TDF exposure was 5.8 (3.2, 7.2), 2.4 (1.4, 3.9) and 2.2 (1.2, 3.8) years. Mean (95% CI) pre, during and post-TDF slopes are given in Table 2. Prior to TDF exposure, a small eGFR decrease of -0.9 (-1.6, -0.2) per year was seen in all patients, with a steeper decrease of -3.1 (-4.6, -1.7) per year during TDF exposure ( $p=0.007$ ). This compares to mean (95% CI) slopes -0.2 (-0.6, 0.3) and 0.3 (0.1, 0.5) pre and during TDF in 5,669 individuals fulfilling the same inclusion criteria who did not discontinue TDF. In those who discontinued, eGFR increased after discontinuation (0.8 (0.1, 1.5) per year). During the first 3 months following initiation and discontinuation, there were steep decreases and increases in slopes (-15.7 (-20.5, -10.9) and 12.5 (8.9, 16.1) respectively). When slopes were stratified by baseline eGFR, those with eGFR <60 had experienced greater decline prior to TDF exposure. During TDF exposure they experienced smaller eGFR declines in the first three months (-2.5 (-17.1, 12.1)  $p=0.32$ ) compared to those with higher eGFR and somewhat greater declines after this point (-8.3 (-18.1, 1.5)  $p=0.43$ ). Recovery appeared greater immediately following TDF discontinuation (23.8 (8.5, 39.0)  $p=0.025$ ) but there were no differences in long-term post-TDF slopes.



### *eGFR Recovery*

Of 834 patients who discontinued TDF with sufficient follow-up to assess recovery, 601 patients (72.1%) experienced eGFR decline during TDF exposure. Median (IQR) eGFR at start and stop of TDF were 94 (81-108) and 77 (57-94). A total of 232 (38.6%) did not recover eGFR after discontinuing TDF, 85 (27.1%) of 314 and 147 (51.2%) of 287 with and without pre-existing eGFR decline respectively. Where eGFR recovery was incomplete, 45 (20.1%), 40 (17.9%), 54 (24.1%) and 85 (37.9%) had an eGFR >90, 75-89, 60-74 and <60 at TDF discontinuation (8 had unknown eGFR at discontinuation). Median (95% CI) time to recovery was 1.3 (1.0, 1.9) years after discontinuation of TDF but recovery may have continued out to 5 years (Figure 2). The median (IQR) eGFR was significantly higher at baseline (97 (86, 110) vs. 92 (77, 106),  $p < 0.0001$ ) and lower at TDF discontinuation (66 (52, 86) vs. 82 (64, 97),  $p < 0.0001$ ) in those with incomplete recovery. A total of 150 (25.0%) individuals were not receiving cART immediately following TDF discontinuation; 22.4% of those with incomplete recovery and 26.6% of those who recovered eGFR. Approximately 59% of those who did and did not recover eGFR were receiving a regimen containing a PI following TDF discontinuation ( $p = 0.95$ ), approximately 16% in both groups received Atazanavir ( $p = 0.99$ ). Whereas 21% of those who experienced recovery received a NNRTI as part of their cART regimen, 31% of those who did not recover eGFR received a NNRTI ( $p = 0.006$ ).

Lower eGFR at discontinuation and higher eGFR at TDF start were independently associated with increased odds of incomplete recovery at 6 months (Table 3). Longer TDF exposure was also associated with increased odds of incomplete recovery. Being on a PI-based regimen (vs. NNRTI) at the start of the TDF episode was associated with decreased odds of experiencing incomplete recovery. Similar results were obtained when recovery was assessed at 12 or 24 months, and when stratified by baseline eGFR < or >90 (data not shown).

In 580 patients who discontinued TDF with an undetectable viral load, mean (95% CI) eGFR slopes pre, during and post TDF were similar to those seen in the whole group (-0.5 (-1.2, 0.1) pre-TDF, -3.4

(-5.2, -1.6) during-TDF, 0.9 (0.2, 1.7) post-TDF) and 41.2% of those with eGFR decline did not recover eGFR during follow up. Factors associated with incomplete recovery in this group were similar to those above; eGFR at TDF start, eGFR at TDF stop and time on TDF, with reduced odds of incomplete recovery when starting a PI-based regimen with TDF (data not shown). Varying the choice of cut off for defining recovery to 10% and 15% meant that only 27.8% and 7% of individuals experienced incomplete eGFR recovery respectively. Using a 10% cut off, the factors associated with incomplete recovery remained unchanged. Using a 15% cut off only eGFR at TDF start and stop were associated with incomplete recovery at 6 months (results not shown).

## Discussion

In this large cohort of predominately white HIV infected men, approximately one quarter of patients discontinued TDF after at least six months exposure. Accelerated eGFR decline was observed during TDF exposure, with substantial recovery in the first 3 months post-TDF discontinuation. Nonetheless, 38% of patients did not recover their eGFR to within 5% of their pre-TDF baseline. An eGFR <75 at TDF start was associated with increased risk of TDF discontinuation while an eGFR <90 at TDF discontinuation was associated with increased risk of incomplete reversibility, as was longer exposure to TDF. These data support renal function monitoring prior to and during TDF exposure, and caution against continued TDF exposure in those with or approaching CKD.

Underlying mechanisms of TDF toxicity have not been fully elucidated. Tenofovir is renally excreted by both glomerular filtration and active tubular secretion. In the proximal renal tubules, TDF is transported across the basolateral membrane via human organic ion transporters 1 and 3 (OAT1 and OAT3)<sup>29</sup> and across the apical membrane via multi-drug resistant proteins 2 and 4 (MRP2 and MRP4)<sup>30</sup>. Tenofovir toxicity has been linked to increased plasma drug concentration<sup>31</sup> and therefore mechanisms which interfere with tenofovir excretion may increase the risk of toxicity. A low GFR will cause impaired TDF filtration; the resulting increased plasma concentrations will promote active

tubular excretion. Polymorphisms in genes such as ABCC4 (encoding MRP4), ABCC2 (encoding MRP2) and ABCC10 (encoding MRP7) are thought to lead to altered TDF handling and intracellular accumulation of TDF<sup>32</sup>. Increased intracellular TDF concentrations are postulated to cause mitochondrial toxicity, with features such as enlargement, depletion and dysmorphic mitochondrial changes seen in severe cases of TDF induced proximal tubulopathy<sup>33</sup>. Increases in TDF plasma levels of approximately 20-30% may also occur during co-administration of TDF with a boosted PI<sup>34</sup>. Clinically, this combination has been associated with worse renal outcomes than TDF and a non-PI containing regime<sup>35-37</sup>. Proposed mechanisms include increased absorption of TDF via PI related inhibition of P-glycoprotein<sup>38</sup> or ritonavir inhibited secretion of TDF via MRP2<sup>39</sup>.

We observed accelerated eGFR decline on TDF in all strata of eGFR, a phenomenon seen in other studies<sup>40,41</sup>. The rapid changes in eGFR seen in the 3 month period following the start and discontinuation of TDF has been noted previously<sup>21,41</sup>. In part, this may be explained by residual tenofovir exposure or co-administered drugs inhibiting tubular creatinine excretion, although we were unable to investigate this in this study. When actual GFR was measured in a study of individuals on cART switching to TDF based regimes, although eGFR declined, there was no change in measured GFR<sup>42</sup>. Beyond the initial three months, the average overall decline in eGFR was modest (-3.1 per year). This is consistent with previous studies which suggest the clinical magnitude of TDF related renal decline was limited. A meta-analysis of TDF vs. non TDF containing regimes demonstrated a mean (95% CI) difference in creatinine clearance between the two groups of only 3.92 (2.13-5.70) mL/min<sup>40</sup> and similarly, in a cohort study with a 10 year follow up, the cumulative eGFR loss attributable to TDF after 4 years was only -3.09 mL/min/1.73m<sup>2</sup><sup>41</sup> but slightly greater than the decline seen within the large US cohort (84% on TDF based regimes) of -1.37 (95% CI -2.02-0.72) mL/min/1.73m<sup>2</sup><sup>25</sup>.

Adverse effects of tenofovir on the kidney are likely the result of tubular injury. Following ischaemic or toxic insult, renal tubular cells may undergo some recovery with reversibility of renal tubular damage as demonstrated in animal models<sup>31</sup> and in observational human studies<sup>43</sup>. In our cohort, approximately 40% of patients with eGFR decline had incomplete eGFR recovery post TDF discontinuation, the majority of whom (62%) had an eGFR <75 when TDF was discontinued. Persistently impaired renal function following TDF discontinuation may reflect irreversible tenofovir-induced kidney damage or progression of underlying CKD. As eGFR at TDF discontinuation was an important predictor of incomplete recovery, the benefits of continued TDF exposure should be reviewed in patients with eGFR <90, and TDF discontinuation should be considered before the eGFR falls below 60, i.e. in those with declining eGFR in the range of 60-75.

We were surprised to note that a lower eGFR at TDF start was protective against incomplete recovery. Although only small numbers of patients started with an eGFR<60, the trend towards a better recovery with a lower eGFR suggests a real phenomenon. This may reflect the findings in the Development of Antiretroviral Therapy (DART) trial, where those with a lower eGFR at baseline had the greatest increase after starting treatment<sup>44</sup>. Alternatively, low eGFR has been linked to increased tenofovir concentration<sup>45</sup>, and therefore withdrawal of a higher tenofovir concentration may allow better eGFR recovery. We feel it unlikely to be due to a low threshold for discontinuation in those with decreased eGFR at TDF start, as time on TDF was taken into account in the analysis.

We observed higher levels of eGFR recovery following TDF discontinuation than previous studies<sup>20,21</sup>. This may be due to our definition of recovery (which considered reductions of up to 5% from baseline), inclusion of discontinuations for any cause, not just suspected TDF toxicity, and taking into account pre-TDF eGFR decline. Using at least two consecutive values to define recovery suggests that our findings are robust and recovery of eGFR following TDF discontinuation is achievable in the majority of patients. Although not complete in all cases, recovery has previously been reported to

continue out to 5-17 months<sup>20-22</sup>. We saw recovery up to 5 years, which may reflect the longer follow up time available. Factors previously associated with greater improvements in eGFR following TDF discontinuation included concomitant PI use<sup>20</sup>, which was postulated to have been due to the withdrawal of TDF at a higher tenofovir plasma concentrations, rapid decline of eGFR within the first month of TDF exposure<sup>21</sup>, and higher nadir and discontinuation CD4 cell counts<sup>22</sup>. In our cohort, we were unable to replicate these findings with the exception of PI use. The latter may reflect that some patients who discontinued TDF plus NNRTI switch to a ritonavir-boosted PI, resulting in enhanced inhibition of MATE-1 mediated tubular creatinine secretion<sup>46</sup>.

Strengths of this study include the use of a large HIV-positive cohort, inclusion of patients who discontinued TDF for any reason, not just toxicity, and prolonged follow up. We took into account pre-TDF renal decline when assessing reversibility of renal decline and variability of eGFR allowing a 5% change from baseline. The 5% change was to account for intra-individual variance of creatinine (reported to be between 4.2-14.4%<sup>47-49</sup>), intra-analytic variance and therefore the calculated coefficient of variance for MDRD or CKD-Epi (4.7%<sup>48</sup> and 7.2%<sup>50</sup> respectively). Using a conservative estimate of variability of 5% we found that the majority of patients recovered eGFR and sensitivity analysis allowing for 10 and 15% variability unsurprisingly improved recovery rates further.

A limitation of this study is the variable frequency of eGFR measurements in this observational setting, with creatinine data unavailable for a substantive section of the cohort. Infrequent eGFR measurements will impact eGFR slopes as estimated by linear regression. However, applying a mixed effects regression model to account for within-subject variability and correlated data produced very similar results. The mean (95% CI) eGFR slope estimates pre, during and post TDF according to mixed effects models were -0.4 (-0.6, -0.2), -3.5 (-4.1, -2.9) and 0.3 (-0.0, 0.6). A total 262 (43.6%) individuals did not recover eGFR during follow up compared to 38.6% according to linear regression models.

We were unable to consider other factors associated with TDF discontinuation such as non-adherence or HIV drug resistance, or factors that may be associated with recovery such as cardiovascular and renal risk factors (diabetes, hypertension and proteinuria), a reliable indicator of muscle mass, clinical and socioeconomic status and the impact of loss to follow up. We cannot exclude the possibility that any observed renal decline is not a TDF effect but due to other drugs. The length of follow up may not have allowed for maximum renal recovery and the lack of access to individual patient records meant that those who stopped for renal toxicity could not be defined. However, when considering only those with an undetectable viral load at TDF discontinuation we did not see any difference in our results.

In conclusion, in those who discontinue TDF, recovery of eGFR is achievable in the majority of patients. Patients with CKD who initiated TDF were at risk of further eGFR decline, while on-going TDF exposure increased the risk of incomplete eGFR recovery. This study supports continued renal monitoring during exposure to TDF and cautions against prolonged TDF exposure in those with declining eGFR.

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**Central Co-ordination:** UCL Research Department of Infection & Population Health, Royal Free Campus, London (Teresa Hill, Susie Huntington, Sophie Josie, Andrew Phillips, Caroline Sabin, Alicia Thornton); Medical Research Council Clinical Trials Unit (MRC CTU), London (David Dunn, Adam Glabay).

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## Footnotes

### (1) Conflicts of Interest

LH has received funding to attend conferences from Gilead Sciences. FAP has received funding to attend conferences or educational meetings, honoraria and/or funding for research from Gilead Sciences, Bristol-Myers Squibb(BMS), Janssen-Cilag, GlaxoSmithKline/ ViiV Healthcare, AbbVie and Merck(MSD). MF has received honoraria and/or funding to attend conferences from: AbbVie, BMS, Gilead, Janssen, Merck, Viiv Healthcare. CL has received honoraria and/or funding from Janssen, Merck, Gilead Sciences, Abbvie, Viiv, Boehringer-Ingelheim(BI) and BMS in connection to conference attendance, consultancy and speaker panels. His unit has received funding from Abbvie, BI, BMS, Janssen and Viiv, for clinical research. RG reports that his department has received research funds from Gilead Sciences. MN has received lecture fees, speaker bureau and research grants from MSD, Gilead Sciences, BMS, Abbott Pharmaceuticals, Viiv Healthcare and BI. PH has received payment for advisory boards and lectures, financial support to attend conferences and his unit has received payment for conducting clinical trials from the following companies involved in marketing anti-retroviral drugs: Abbott Pharmaceuticals, BI, BMS, Gilead Sciences, Johnson and Johnson (Tibotec), Viiv (GSK and Pfizer). RJ has received funding to attend conferences or educational meetings, honoraria and/or funding for research from Gilead, BMS, Janssen-Cilag, GlaxoSmithKline/ ViiV Healthcare and Abbvie. DC has received speakers fees from BMS. CAS has received funding from Gilead Sciences, BMS, Abbott Pharmaceuticals, Viiv Healthcare, Janssen-Cilag and MSD for membership of Data Safety and Monitoring Boards, Advisory Boards, Speaker Panels and for the development of educational materials. SJ, TH, DN, JW, LC and MJ have no conflicts of interest to declare.

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**(3) Previous presentation of this work**

Previous versions of this work have been presented at the 11<sup>th</sup> HIV Drug Therapy Conference, November 2012 in Glasgow, UK and at the 20<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI), March 2013 in Atlanta, GA.

**(4) Corresponding Author:**

Miss Sophie Jose

Research Department of Infection and Population Health

UCL, Royal Free Campus

Rowland Hill Street

London NW3 2PF

Telephone 02077940500 ext. 36763

Email: [sophie.jose@ucl.ac.uk](mailto:sophie.jose@ucl.ac.uk)

**(5) Author affiliations are as listed on the title page of the manuscript**

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## List of Tables and Figures

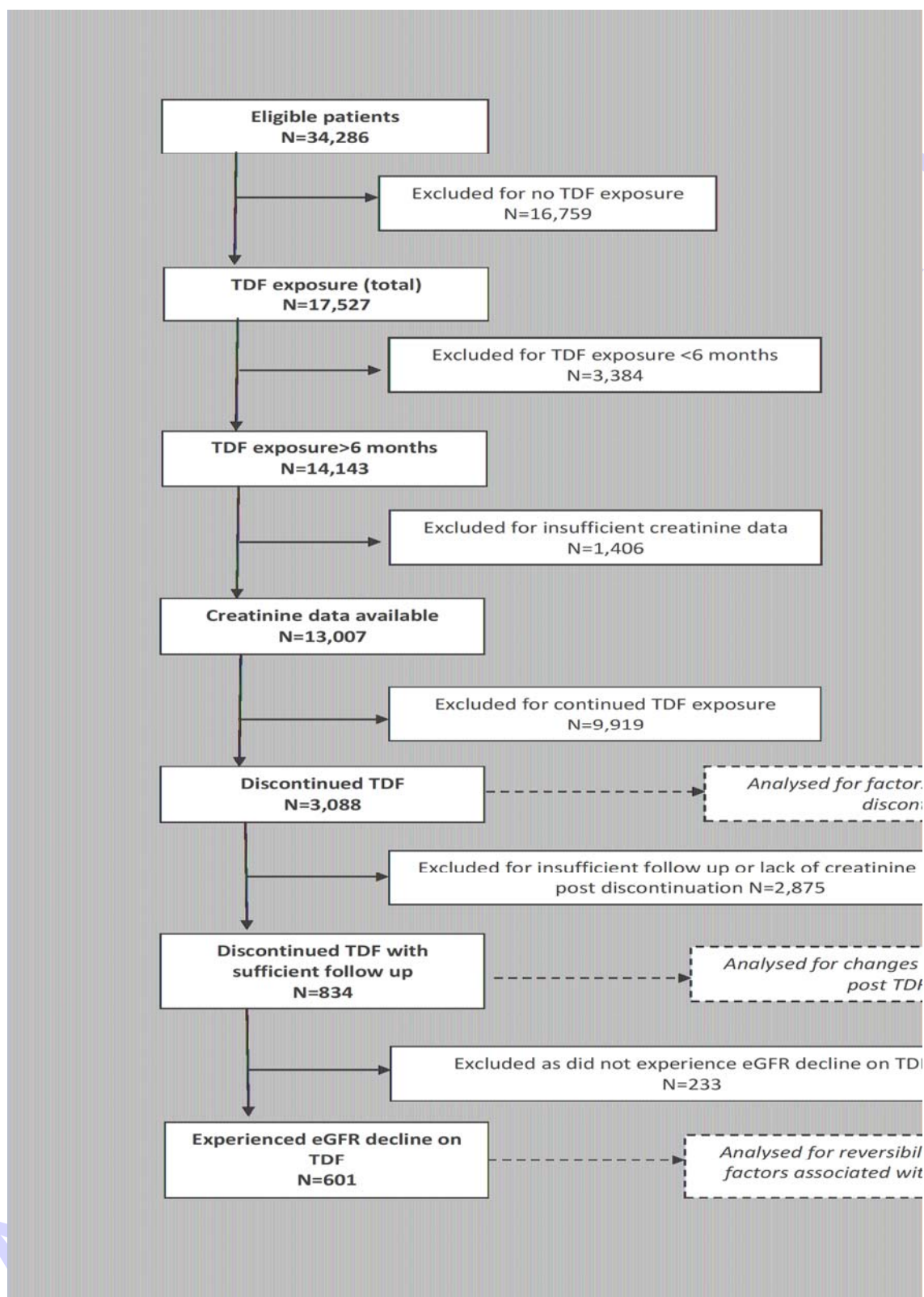
**Figure 1:** Selection of cases for analysis

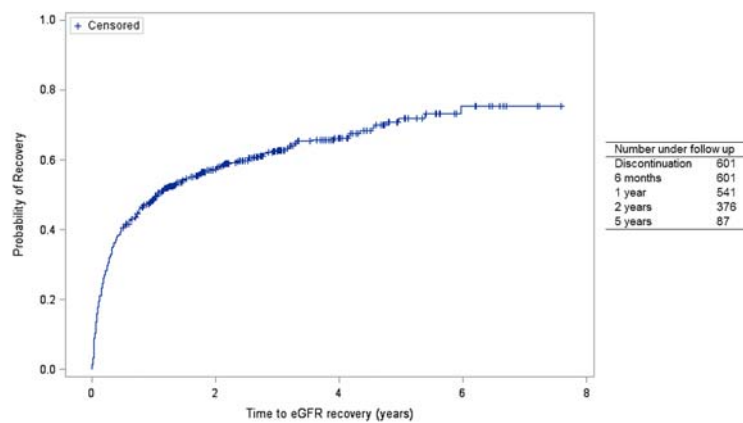
**Table 1:** Characteristics of patients in UK CHIC dataset with at least 6 months tenofovir exposure

**Table 2:** Mean (95% CI) eGFR slopes (ml/min/1.73m<sup>2</sup>/year) before, during and after tenofovir exposure, estimated from piecewise linear regression model

**Figure 2:** Kaplan-Meier plot showing cumulative proportion of individuals who discontinued TDF following a decline in eGFR that experienced eGFR recovery following discontinuation

**Table 3:** Results from univariable and multivariable logistic regression model showing factors associated with incomplete eGFR recovery at 6 months after discontinuation of tenofovir





**Table 1:** Characteristics of patients in UK CHIC dataset with at least 6 months tenofovir exposure

Characteristic at TDF start	N	(%)
<b>Sex</b>		
Male	10550	81.1
<b>Ethnicity</b>		
White	8300	63.8
Black	3026	23.3
Other/unknown	1681	12.9
<b>Exposure</b>		
Homosexual/bisexual	8236	63.3
Heterosexual	3713	28.6
IDU	356	2.7
Other/unknown	702	5.4
<b>Calendar year at TDF start</b>		
1999-2003	2482	19.1
2004-2007	3992	30.7
2008-2010	6533	50.2
<b>Previous exposure to TDF</b>		
Yes	603	4.6
<b>ART-naïve at TDF start</b>		
Yes	4466	34.4
<b>ARV regimen class at TDF start</b>		
PI-based (no ATZ)	2690	20.7
PI-based (with ATZ)	1329	10.2
NNRTI-based	7098	54.6
NRTIs only		
Other	1890	14.5
<b>Previous AIDS event</b>		
Yes	3053	23.5
<b>HBV status at TDF start</b>		

Negative	8412	64.7
Positive	599	4.6
Not tested	3996	30.7
<b>HCV status at TDF start</b>		
Negative	8619	66.3
Positive	730	5.6
Not Tested	3658	28.1
<b>eGFR at TDF start (ml/min/1.73m<sup>2</sup>)<sup>1</sup></b>		
<60	166	1.4
60-74	985	8.5
75-89	2572	22.1
>90	7898	68.0
	<b>Median</b>	<b>(IQR)</b>
<b>Age (years)</b>	40	34 - 46
<b>CD4 cell count (cells/mm<sup>3</sup>)</b>	303	190 - 482
<b>Viral Load (log<sub>10</sub>copies/ml)</b>	2.9	1.7 – 4.7

**TDF**=Tenofovir; **IDU**=Injecting drug use; **PI**=Protease inhibitor; **NNRTI**=Non-nucleoside reverse transcriptase inhibitor; **NRTI**=Nucleoside reverse transcriptase inhibitor; **ATZ**=Atazanavir; **HBV**=Hepatitis B virus; **HCV**=Hepatitis C virus.

<sup>1</sup> n=11,621.

**Table 2:** Mean (95% CI) eGFR slopes (ml/min/1.73m<sup>2</sup>/year) before, during and after tenofovir exposure, estimated from piecewise linear regression model

	Overall	Start eGFR (ml/min/1.73m <sup>2</sup> )		
		<60	60-89	≥90
<b>N</b>	823	24	322	477
<b>Pre-TDF</b>	-0.9 (-1.6, -0.2)	-5.2 (-8.4, -2.0)	-1.4 (-2.2, -0.5)	-0.4 (-1.5, 0.6)
<b>During TDF</b>				
<b>≤3 months</b>	-15.7 (-20.5, -10.9)	-2.5 (-17.1, 12.1)	-16.9 (-27.0, -6.8)	-15.3 (-19.9, -10.7)
<b>&gt;3 months</b>	-3.1 (-4.6, -1.7)	-8.3 (-18.1, 1.5)	-2.6 (-5.5, 0.4)	-3.3 (-4.8, -1.8)
<b>Post-TDF</b>				
<b>≤3 months</b>	12.5 (8.9, 16.1)	23.8 (8.5, 39.0)	15.8 (10.0, 21.6)	9.5 (4.7, 14.3)
<b>&gt;3 months</b>	0.8 (0.1, 1.5)	-0.4 (-6.4, 5.7)	0.3 (-0.8, 1.4)	1.2 (0.12, 2.1)

**Table 3:** Results from univariable and multivariable logistic regression model showing factors associated with incomplete eGFR recovery at 6 months after discontinuation of tenofovir

	Univariable			Multivariable		
	OR	95% CI	P	OR	95% CI	P
<b>Age at TDF start</b> (per 10 year increase)	1.13	(0.95, 1.34)	0.17	1.00	(0.80, 1.24)	0.57
<b>Sex</b>						
Male	1.00	-	-	1.00	-	-
Female	0.67	(0.43, 1.03)	0.070	0.95	(0.52, 1.74)	0.87
<b>Ethnicity</b>						
White	1.00	-	-	1.00	-	-
Black	0.59	(0.38, 0.92)	0.020	0.82	(0.45, 1.52)	0.53
Other/Unknown	1.00	(0.57, 1.76)	0.99	1.06	(0.57, 1.96)	0.85
<b>Exposure</b>						
<i>Homosexual/bisexual</i>	1.00	-	-			
<i>Heterosexual</i>	0.75	(0.51, 1.10)	0.14	-	-	-
<i>IDU</i>	0.63	(0.29, 1.34)	0.29			
<i>Other/Unknown</i>	1.00	(0.32, 3.11)	1.00			
<b>ART-Naïve at TDF start</b>						
No	1.00	-	-			
Yes	0.93	(0.55, 1.57)	0.78			
<b>Regimen class at TDF start</b>						
NNRTI	1.00	-	-	1.00	-	-
PI	0.70	(0.48, 1.02)	0.066	0.60	(0.39, 0.91)	0.018
Other	0.75	(0.49, 1.14)	0.18	0.69	(0.43, 1.11)	0.13
<b>CD4 count at TDF stop</b> (per 50cells/mm <sup>3</sup> increase)	1.01	(0.98, 1.05)	0.37	-	-	-
<b>Undetectable viral load at TDF stop</b>						
No	1.00	-	-	1.00	-	-

Yes	1.39	(0.93, 2.04)	0.087	0.96	(0.63, 1.48)	0.86
<b>eGFR at TDF start (ml/min/1.73m<sup>2</sup>)</b>						
≥90	1.00	-	-	1.00	-	-
75-90	1.10	(0.74, 1.64)	0.65	0.47	(0.28, 0.78)	0.004
60-74	0.61	(0.38, 0.99)	0.046	0.14	(0.07, 0.27)	<0.0001
<60	0.24	(0.08, 0.69)	0.008	0.04	(0.01, 0.15)	<0.0001
<b>eGFR at TDF stop (ml/min/1.73m<sup>2</sup>)</b>						
≥90	1.00	-	-	1.00	-	-
75-90	1.59	(1.02, 2.51)	0.043	2.18	(1.31, 3.62)	0.003
60-74	2.38	(1.49, 3.80)	0.0003	4.81	(2.61, 8.89)	<0.0001
<60	2.96	(1.89, 4.65)	<0.0001	13.18	(6.29, 27.6)	<0.0001
<b>Time on TDF (per year increase)</b>	1.20	(1.09, 1.32)	0.0003	1.15	(1.03, 1.28)	0.012

**OR**=Odds Ratio; **95% CI**= 95% Confidence Interval; **P**=p-value.

**TDF**=tenofovir; **IDU**=injecting drug use; **NRTI**= nucleoside reverse transcriptase inhibitor; **NNRTI**=non-nucleoside reverse transcriptase inhibitor; **PI**=protease inhibitor